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| 10/505,191 | 06/24/2005 | Jeffrey P. Erickson | AIB-09206 | 5158 |

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| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/505,191 | ERICKSON, JEFFREY P. | |
| | Examiner | Art Unit | |
| | MAGDALENE K. SGAGIAS | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13,15-29,32-35 and 41-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13,15-29,32-35 and 41-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicant's arguments filed 10/13/08 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-13, 15-29, 32-35, 41-56 are pending and under consideration. Claims 14, 30-31, 36-40 are canceled.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 15-29, 32-35, 41-56 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a transgenic non-human mammal whose genome comprises an exogenous nucleic acid encoding at least one transgenic polypeptide, said nucleic acid operably linked to a salivary gland-specific cis-acting transcription control region ranging between about 4.6 KB- 30kB, wherein said polypeptide is produced in said mammal's at a level of at least 0.5 mg/ml, a method of collecting saliva from the same transgenic non-human mammal, and a method of producing the same transgenic non-human mammal.

The specification has asserted that the invention features transgenic non-human mammals that express transgenic polypeptides in their saliva. The specification discusses that salivary gland and saliva specific regulatory elements are necessary to achieve saliva specific expression of a polypeptide of interest. See pages 26-28 of the specification. However, the

guidance provided by the specification does not correlate to use of any particular saliva specific regulatory element for the creation of transgenic non-human mammals embraced by the claims. Moreover, the guidance provided by the specification is general as it does not even disclose which saliva regulatory elements could be used to create any of the transgenic non-human mammals embraced by the claims. Finally, the working examples provided by the specification (see pages 81-101) while exemplifying creation of different transgenic cows that express prothrombin and fibrinogen in their saliva respectively, did not disclose which saliva regulatory elements were used to create the transgenic cows and therefore failed to provide the skilled artisan with adequate guidance to make any of the transgenic non-human mammals embraced by the claims. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, the claims embrace transgenic non-human mammals that express and produce a transgenic polypeptide in saliva. The specification has discussed that saliva specific regulatory elements are necessary to achieve expression of a polypeptide of interest in saliva of a transgenic non-human mammal. See pages 26-29 of the specification. However, the guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (PSP and B1-Ips genes) (p 27-28) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva. This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217,

which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson. Finally, in an attempt to provide guidance as to which saliva regulatory sequence may be used within the scope of the claimed invention, the specification has relied on improper incorporation by reference of subject matter that appears to be essential. See the references to Mikkelsen, Larson and Mirels at pages 27-28 of the specification. Applicant is reminded that subject matter essential to the claimed invention may not be incorporated by reference to a non-patent publication. See 37 C.F.R. 1.57(c) and MPEP 608.01(p). In addition, the specification while is suggesting Mikkelsen and co-workers described techniques for manipulating gene expression in a transgenic animal to engender secretion of a gene product into saliva suitable for use in certain aspects of the present invention for production of desired substances in saliva of genetically engineered animals and suggest Mikkelsen et al. (1992), Nature 20(9): 2249-2255, which is incorporated herein by reference and further suggest the mouse PSP gene has been cloned and characterized by Shaw and Schibler, and by Poulsen and co-workers and suggest the region of 5' flanking DNA required for salivary gland-specific expression is about 4.6 kb; but, longer regions, extending farther upstream may provide higher levels of expression [0063], however, the specification has failed to provide guidance to a salivary gland-specific cis-acting transcription control region ranging between about 4.6 KB- 30kB, which has defined bounds of ranging between about 4.6 KB- 30kB, resulting in the production of the claimed amount of saliva in a transgenic non-human animal. The declaration provided by Wheeler has provided evidence that a transgenic doe was birthed that has been shown to be transgenic with transfected gene consisting of the bSP30a promoter and the human serum albumin gene. The declaration shows evidence of secretion of the human serum albumin into the transgenic doe's saliva and the

transgene is expressed in the salivary gland as evidenced by Western blot analysis. However, the Western blot analysis has not provided evidence that the polypeptide is produced in said doe's saliva at a level of at least 0.5 mg/ml as claimed in the instant claims. **Lubon et al,** [Transfusion Medicine Reviews, X(2): 131-143, 1996 (IDS)] while reviewing the targeted expression of transgenes in transgenic animals by fusing their DNA with coding sequences to promoters of genes note many factors including cis-acting elements of gene regulatory regions, intragenic and coding sequences of heterologous genes, and the chromosomal integration site influence the tissue-specific and developmental regulation of transgenes as well as their expression (p 132, 2nd column, last paragraph). Lubon et al note in the transgenic approach, synthesis of a recombinant protein targeted to a selected cell type or organ, enabling the product to be harvested from body fluids like milk, blood, **saliva,** or urine questions with respect to transgene inheritance and stability, appropriate posttranslational modifications on heterologous proteins, industrial production procedures, and regulatory affairs have now emerged, as there are limited data published on the long-term effects of foreign protein expression on transgenic animal "bioreactor" (TAB) (abstract). Limitations will be encountered in the amount of heterologous protein expressible, as tissues synthesizing milk, blood, urine, or **saliva** need to contain some proportion of endogenous proteins for secretion and function (p 136, 1st column, 1st paragraph). Leakage may restrict the expression of certain proteins in the TAB as potential deleterious systemic effects can be envisaged for proteins of potent biological activity, such as erythropoietin, tPA, or human growth hormone (p 136, 1st column, 1st paragraph. Accordingly, given the lack of guidance provided by the specification, the skilled artisan would not know which regulatory sequence to use to achieve saliva specific expression of a polypeptide in a transgenic non-human mammal. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make

and use any of the transgenic non-human mammals embraced by the claims without a reasonable expectation of success.

As a second issue, while the claims embrace transgenic non-human mammals expressing a transgenic polypeptide in saliva, the working examples provided by specification did not provide adequate guidance that would enable one of skill in the art to create any of the transgenic non-human mammals embraced by the claims. The working examples (see pages 81-101 of the specification) discussed the creation of separate transgenic cows that expressed prothrombin and fibrinogen respectively in their saliva. However, the working examples failed to disclose which saliva regulatory elements were used in the creation the transgenic cows. As previously stated the specification as a whole has not even identified or provided the regulatory elements necessary to practice the claimed invention. A mere statement that saliva regulatory elements existed and could be used is not sufficient to enable the breadth of the claims as directed to transgenic non-human mammals expressing transgenic polypeptides in saliva. If there is no disclosure of starting material or of any conditions under which claimed process can be carried out, undue experimentation is required, and there is failure to meet enablement requirement that cannot be rectified by asserting that all disclosure related to process is within skill of art. See Genentech Inc. v. Novo Nordisk A/S 42 USPQ2d 1001, 1997. The art teaches that parotid-specific transgene expression requires an upstream cis-regulatory domain, namely the parotid control region, and this parotid control region functions with a heterologous promoter and is indispensable for achieving transgene expression and deletion of specific regions results in ectopic gene expression and the inducible expression of the transgene expression in transgenic mice decreases over 30-fold (abstract) (**Tu et al**, Gene Expr, 3(3): 289-305, 1993). In this case the starting material that has not been disclosed is the saliva regulatory element necessary to create the transgenic non-human mammals embraced by the claims. Given, the

lack of guidance and absence of working examples provided by the specification correlating to creation of transgenic non-human mammals, the lack of guidance provided by the specification with respect to use of saliva regulatory elements, the unpredictability of saliva regulatory elements, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Applicants argue they have provided two Declarations demonstrating that: i) a transgenic goat was created using a parotid secretory protein (PSP) promoter (i.e., BSP30a) that secrets an exogenous protein in saliva; and ii) that the sequences of BSP30a were known at the time of filing of the pending application.

These arguments are not persuasive because: i) the Western blot analysis of saliva and serum of the transgenic goat while it provides evidence that the protein is expressed in the tested samples, however, it does not provide evidence that the protein is produced in said goat's saliva at a level of at least 0.5 mg/ml as claimed in the instant claims; ii) the issue is not the availability of the sequences of BSP30a for the creation of the calimed transgenic mammal rather the issue is whether the BSP30 promoter in any transgenic mammal will effectively produce 0.5 mg/ml of the transgene protein product secreted in the saliva. Applciant's have not provided evidence to such an effect. For example, as discussed above the art teaches that targeted expression of transgenes in transgenic animals by fusing their DNA with coding sequences to promoters of genes note many factors including cis-acting elements of gene regulatory regions, intragenic and coding sequences of heterologous genes, and the chromosomal integration site influence the tissue-specific and developmental regulation of transgenes as well as their expression. The transgenic approach, synthesis of a recombinant protein targeted to **saliva**, questions with respect to transgene inheritance and stability, appropriate posttranslational modifications on heterologous proteins, have now emerged, as

there are limited data published on the long-term effects of foreign protein expression on transgenic animal as a "bioreactor". Limitations will be encountered in the amount of heterologous protein expressible, as tissues synthesizing **saliva** need to contain some proportion of endogenous proteins for secretion and function. Leakage may restrict the expression of certain proteins in the transgenic animal as potential deleterious systemic effects can be envisaged for proteins of potent biological activity, such as erythropoietin, tPA, or human growth hormone.

Applicants argue the amendment to identify the upper range of the 5' flanking region as "30 kb", as enabled by the 6,140,522 patent. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application. Further, the secretory promoters disclosed in '522 patent are capable of secreting transgenic proteins in saliva: Transgenesis may also by detected by assaying for expression of the recombinant polypeptide in a tissue, secretion (e.g., saliva), or other body fluid. In the case where the goal is expression of a recombinant polypeptide in milk of cows it will be especially useful to assay the saliva of bulls for expression levels. This is because some mammary specific promoters may also cause salivary gland expression, albeit at low levels. See, e.g., Archibald et al. (1990) Proc. Nat. Acad. Sci. USA 87Z:5178-5182. '522 patent, col 19 ln 19-27. In fact, the '522 patent discloses a promoter construct that results in creation of a transgenic cow producing transgenic protein in saliva. See, Example 26.

These arguments are not persuasive because patent '522 teaches a mozaic and not a transgenic animal that secretes the trangene product in the saliva, wherein it is cited that expression of recombinant protein in saliva of calves ten animals were born from oocytes co-injected with the hLF transcgene and a hLZ transgene none of these animals appeared

transgenic as judged by Southern Blot, but four of them (all males) were judged to be mosaic based on PCR with 0.5 .mu.g DNA from blood and ear (see example 26) (emphasis added). Patent '522 teaches the mosaic animal that secretes the transgene into the saliva is comprised of the designed expression vector 16,8hLZ, where the 5' flanking region (including the promoter) of the hLZ gene was removed and replaced with the bovine .alpha.S1 casein gene promoter by subcloning into the plasmid p-16kb CS which is designed by fusion site is located in the 5' UTR of the hLZ gene (exon 1), such that in addition to 23 bp of casein 5' UTR most of the hLZ 51 UTR is present. All coding sequences in this construct, including the signal sequence, are derived from hLZ clone. Applicants have not provided evidence to correlate the mosaic transgenic animal comprised of the bovine casein promoter and the hLZ transgene that secretes the transgene product in the saliva to the claimed transgenic mammal secreting the transgene at a level of 0.5 mg/ml.

As discussed in the previous office action mailed on 4/14/08 Applicants by simply contemplating that using promoters that are ranging between about 4.6 kB- 30kB does not provide any guidance for any boundaries for designing the claimed salivary gland-specific transcription control region of ranging between about 4.6 kB- 30kB. An artisan will not be able to design specific salivary gland 5' flanking DNA required for salivary gland specific expression without set sequence boundaries. Applicants have not disclosed what are the regulatory sequences necessary to achieve saliva specific expression and secretion of a polypeptide of interest in a transgenic mammal saliva at the claimed levels. Applicants have not correlated the use of parotid gland expression cassette, carrying all known regulatory regions in the Psp gene to the expression of a heterologous protein in the saliva of a transgenic mammal to overcome the art limitations of using the "known" promoter sequence of the parotid secretory protein (PSP)

gene as discussed by Samuelson. Applicants have not disclosed the main regulatory region or enhancer in the murine PSP gene to achieve the expression of a claimed polypeptide in a transgenic mammal. Note the specification recognizes the importance of regulatory sequences, in addition to the promoter sequences such as enhancers, splice signals, transcription termination signals and polyadenylation sites, among others which are useful regulatory sequences that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms." (see specification p 34). Note the specification points to the importance of the regulatory sequences besides the promoter for the claimed invention by emphasizing: "Among the sequences that regulate transcription that are useful in the invention, in addition to the promoter sequences discussed above, are enhancers, splice signals, transcription termination signals and polyadenylation sites, among others. Particularly useful regulatory sequences include those that increase the efficiency of expression of the polypeptide and/or protein of interest in transgenic organisms. Also particularly preferred in this regard are those that increase the specificity of expression in targeted compartments of a transgenic organism. Among highly particularly preferred regulatory regions in this regard are those that increase the efficiency, the specificity or both the efficiency and the specificity of expression in salivary glands, and the production of a desired substance thereby in the saliva of transgenic non-human animals in accordance with the invention." (see specification p 34-35). The guidance provided by the specification with respect to use of saliva specific regulatory elements was general and did not specifically relate to use of any particular regulatory sequence. Moreover, the specification while suggesting that certain regulatory elements (from PSP and B1-Ips genes) could be used failed to disclose the actual nucleotide sequences of such elements, which could direct a high level of transgene expression in saliva.

These arguments are not persuasive because at the time of filing the specification fails to correlate the endogenous expression of BSP3a and BSP30b to exogenous expression of BSP30a and BSP30b in a non-human mammal's saliva producing 0.5 mg/ml of a polypeptide in all non-human mammals as claimed in the instant application. While the Erickson declaration describes the expression of both BSP30a and BSP30b is restricted to salivary gland tissue, however the specification fails to provide guidance to an exogenous nucleic acid encoding at least one transgenic polypeptide, wherein said nucleic acid operably linked to a BSP30a or BSP30b salivary gland-specific cis-acting transcription control regions, wherein said polypeptide is produced in a non-human mammal's saliva at a level of at least 0.5 mg/ml as claimed in the instant application. The citation in the specification, p 27 that expression control regions from the gene for parotid secretory proteins ("PSP") are suitable to engineer salivary-gland specific gene expression, in the manner Mikkelsen and so-workers used control regions from the gene for mouse PSP ("moPSPW) to engender parotid-specific transgenic expression in mice, **does not** provide guidance for a BSP30a or BSP30b salivary gland-specific cis-acting transcription control regions. Moreover, the transgenic goat as disclosed in the Erickson declaration does not disclose the production of the polypeptide is produced in saliva at a level of at least 0.5 mg/ml as claimed in the instant application. As discussed in the previous office action mailed 3/26/07 pages 6-8 for example, "……..This is an important point because the prior art has set forth that regulatory sequences of genes expressed in the cells of salivary gland are basically undeveloped and failed to direct high levels of polypeptide expression. See Samuelson (Annu. Rev. Phys., 1996, 58: 209-229), for example on page 217, which discussed the limitations of using the "known" promoter sequence of the parotid secretory protein (PSP) gene. Also, Samuelson provided an extensive review of the limitations of known salivary gland promoters. See throughout Samuelson.

These arguments are not persuasive because the availability of the bovine salivary protein sequence gene and protein as accession numbers in the Gene Bank does not overcome the lack of guidance for specific regulatory sequences that are salivary gland specific cis-acting transcription control region of at least 4.6 kB-30 kB, resulting in any transgenic non-human mammal producing the claimed amount of a polypeptide in any non-human mammal.

***Conclusion***

**No claim is allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Information regarding the

status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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